



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification:</b> <b>A61K 9/72, 9/12, 47/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 86/ 04233</b> <b>(43) International Publication Date:</b> 31 July 1986 (31.07.86)
<b>(21) International Application Number:</b> PCT/GB86/00001 <b>(22) International Filing Date:</b> 2 January 1986 (02.01.86) <b>(31) Priority Application Number:</b> 8501015 <b>(32) Priority Date:</b> 16 January 1985 (16.01.85) <b>(33) Priority Country:</b> GB  <b>(71) Applicant (for all designated States except US):</b> RIKER LABORATORIES, INC. [US/US]; 19901 Nordhoff Street, Northridge, CA 91324 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> JINKS, Philip, Anthony [GB/GB]; 37 Glebe Close, Mountsorrel, Leicestershire (GB). BELL, Alexander [GB/GB]; 15 Marton Road, Chilwell, Beeston, Nottinghamshire (GB). FISCHER, Franz, Xaver [AT/CH]; Hoehenstrasse 27, CH-4125 Riehen (CH).		<b>(74) Agent:</b> LLOYD WISE, TREGEAR & CO.; Norman House, 105-109 Strand, London WC2R OAE (GB).  <b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> DRUG-CONTAINING CHLOROFLUOROCARBON AEROSOL PROPELLENT FORMULATIONS  <b>(57) Abstract</b>  Complete dissolution of a wide range of drugs in chlorofluorocarbon aerosol propellents is achieved by the presence of glycerol phosphatides, preferably phosphatidylcholine.		

***FOR THE PURPOSES OF INFORMATION ONLY***

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GA	Gabon	MR	Mauritania
AU	Australia	GB	United Kingdom	MW	Malawi
BB	Barbados	HU	Hungary	NL	Netherlands
BE	Belgium	IT	Italy	NO	Norway
BG	Bulgaria	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	LI	Liechtenstein	SN	Senegal
CH	Switzerland	LK	Sri Lanka	SU	Soviet Union
CM	Cameroon	LU	Luxembourg	TD	Chad
DE	Germany, Federal Republic of	MC	Monaco	TG	Togo
DK	Denmark	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali		
FR	France				

-1-

DRUG-CONTAINING CHLOROFLUOROCARBON AEROSOL  
PROPELLENT FORMULATIONS

- 5           This invention relates to medicinal aerosol formulations and in particular to drug-containing chlorofluorocarbon aerosol propellant formulations for topical or for endopulmonary or nasal inhalation administration.
- 10           Medicinal aerosol formulations generally contain a mixture of chlorofluorocarbons, e.g. trichloromonofluoromethane (Propellant 11), dichlorotetrafluoroethane (Propellant 114) and dichlorodifluoromethane (Propellant 12). The drug is
- 15 either present as a solution in the aerosol formulation or as a dispersion of fine particles. For endopulmonary or nasal inhalation, particles predominantly in the size range 2 to 5 microns are required.
- 20           There are very few drugs which can be solubilised in chlorofluorocarbon aerosol propellents alone. Generally, it is necessary to utilise a polar co-solvent, such as ethanol, in order to achieve solubilisation of the drug. However, the resulting
- 25 solutions can be chemically unstable due to reaction between the co-solvent and the drug or the co-solvent and the propellant system.
- Furthermore, when large proportions of co-solvent, e.g. ethanol, are required to achieve
- 30 dissolution of the drug, the resulting spray droplet size may be too large for certain applications, in particular, endopulmonary inhalation therapy.

=2=

Suspension of drug in aerosol propellents is achieved by pulverising the drug into the desired particle size range and thereafter suspending the particles in propellents with the aid of a surfactant.

- 5 The disadvantages of this technique are that drug particles may agglomerate, grow in size or become adsorbed onto the surface of the container in which the formulations are stored prior to dispensing. Furthermore, it is necessary to agitate the product  
10 prior to use in order to ensure dispersion of the formulation and uniformity of dosage.

The present invention provides an alternative technique for incorporating drugs into chlorofluorocarbon aerosol propellents.

- 15 Therefore according to the invention there is provided an aerosol formulation comprising one or more chlorofluorocarbon aerosol propellents, a glycerol phosphatide and a drug, the drug being dissolved in the composition.

- 20 The glycerol phosphatide may be any one of the following compounds; phosphatidylcholine (lecithin), phosphatidylethanolamine (cephalin), phosphatidylinositol, phosphatidylserine, diphosphatidylglycerol or phosphatidic acid.

- 25 Surprisingly it has been found that glycerol phosphatides cause complete dissolution of certain drugs in chlorofluorocarbon propellents. Phosphatidylcholine (lecithin) has been utilised as a surfactant in aerosol formulations containing suspended  
30 drug particles but heretofore it has not been appreciated that this particular compound can enhance the solubility of certain drugs in chlorofluorocarbon propellents.

=3=

It has been found that drugs having at least very slight solubility in chlorofluorocarbon propellents will exhibit an enhanced solubility in the chlorofluorocarbon propellant in the presence of glycerol phosphatide. It is postulated that this enhanced solubility is attributable to drug in true solution becoming associated with reverse micelles of the glycerol phosphatide which allows further drug to dissolve in the propellant. Thus, the solubilisation process is believed to be as follows:

drug	$\xrightleftharpoons{\hspace{1cm}}$	drug in solution in propellant	$\xrightleftharpoons{\hspace{1cm}}$	drug associated with reverse micelles of glycerol phosphatide
		Initial solubilisation		Micellar solubilisation

15

Whilst the compositions of the invention appear visibly to be true solutions since there is no dispersed phase apparent, they are more correctly micellar solutions.

The formulations of the invention may be prepared by forming a concentrate of glycerol phosphatide with a drug and Propellant 11. The concentrate may be formed by simple admixture with agitation and optionally under heating, e.g. 50°C, until complete dissolution of the drug has been attained. The concentrate may then be mixed with the remainder of the propellant formulation, e.g. Propellents 12 and 114.

Phosphatidylcholine is the most suitable glycerol phosphatide to use in view of its low toxicity and high drug solubilising efficacy. Phosphatidylcholine purified from soya bean lecithin is readily available commercially and suitable grades include Epikuron 200 (Lucas-Meyer) and Lipoid S100

30

-4-

(Lipoid KG). Both products have a phosphatidylcholine content in excess of 95%

It has been found that certain drugs which are practically insoluble in chlorofluorocarbon propellents alone can be solubilised in the propellant/glycerol phosphatide system by the addition of a small amount of a co-solvent such as ethanol.

It is postulated that the co-solvent enhances the initial solubilisation step of the solubilisation process. Certain commercially available forms of lecithin, in addition to their phosphatidylcholine content, contain ethanol as an impurity. With compounds of this type, e.g. Lipoid S45, the ethanol may likewise enhance drug solubilisation.

Suitable drugs for use in the invention comprise those compounds which exhibit at least a very slight solubility in a chlorofluorocarbon propellant. In general, the drug will be in the form of an ester, base or free alcohol. Highly polar ionic salts of drugs are less suitable since it may not be possible to solubilise the drug in sufficient quantity even with the presence of a small amount of co-solvent.

Exemplary drugs include steroids, e.g. beclomethasone dipropionate, betamethasone dipropionate, acetate, valerate and free alcohol. Other drugs include salbutamol base, atropine base, prednisolone, formoterol base, hydrochloride, fumarate and hemisulphate.

Further suitable drugs for use with the invention include the following:

Anorectics: e.g. benzphetamine hydrochloride  
chlorphentermine hydrochloride

=5=

- Anti-depressants: e.g. amitriptyline hydrochloride  
imipramine hydrochloride
- Anti-hypertensive agents: e.g. clonidine hydrochloride
- Anti-neoplastic agents: e.g. actinomycin C
- 5 Anti-cholinergic agents: atropine base
- Dopaminergic agents: e.g. bromocriptine mesylate
- Narcotic analgesics: e.g. buprenorphine hydrochloride
- Beta-adrenergic blocking agents: e.g. propranolol  
hydrochloride
- 10 Corticosteroids: e.g. lacticortone, hydrocortisone,  
fluocinolone acetonide,  
triamcinolone acetonide
- Prostaglandins: e.g. dinoprost trometamol
- Sympathomimetics: e.g. xylometazoline hydrochloride
- 15 Tranquillisers: e.g. diazepam, lorazepam
- Vitamins: e.g. folic acid, nicotinamide
- Brochodilators: e.g. clenbuterol hydrochloride  
bitolterol mesylate
- Sex hormones: e.g. ethinyloestradiol, levonorgestrel.
- 20 The ratio of drug : glycerol phosphatide :  
cosolvent (if required) : chloro-fluorocarbon  
propellant depends upon a number of criteria:
- 1) The concentration of drug required in the final  
formulation.
  - 25 2) The solubility of glycerol phosphatide in the  
particular blend of chlorofluorocarbon  
propellents.
  - 3) The droplet size and evaporation characteristics  
required of the emitted spray. For inhalation  
purposes the optimum levels of glycerol  
30 phosphatide and Propellant 11 will be the  
minimum permissible levels to achieve a stable  
solution. Higher levels of these components

=6=

result in an increase in the droplet size of the spray upon dispensing due to a lowering of the volatility of the formulation.

- 4) Solubility of the drug in the propellents or  
5 propellent/co-solvent.

A wide range of propellents may be used in the formulations of the invention including:

- Propellent 11 trichloromonofluoromethane  
Propellent 12 dichlorodifluoromethane  
10 Propellent 13 monochlorotrifluoromethane  
Propellent 21 dichloromonofluoromethane  
Propellent 22 monochlorodifluoromethane  
Propellent 113 trichlorotrifluoroethane  
Propellent 114 dichlorotetrafluoroethane  
15 Propellent 115 monochloropentafluoroethane  
Propellent 500 azetrope - 73.8% dichlorodifluoromethane  
and 26.2% 1,1-difluoroethane

- In addition to chlorofluorocarbon aerosol  
propellent the formulations may contain other  
20 propellents, e.g. DME (dimethylether).

In general, the compositions comprising drug, glycerol phosphatide and propellent may be made within the following general weight ratios:

- 25 drug : glycerol phosphatide  
1 to 500 : 100  
glycerol phosphatide : propellent  
0.01 to 20 : 100

- For many drugs the weight ratio of drug:glycerol phosphatide will generally be in the range 1 to 30:100  
30 and that of glycerol phosphatide:propellent in the range 0.01 to 10:100. Preferably the weight ratio of drug:glycerol phosphatide will be in the range 2 to 10:100 and that of glycerol phosphatide:propellent in the range 0.01 to 3:100.



=7=

The invention will now be illustrated by the following Examples.

Example 1

5 Solubilisation of beclomethasone dipropionate

	<u>mg/ml</u>
(a) beclomethasone dipropionate	1
(b) Epikuron 200	14
(c) Propellant 11	270
10 (d) Propellant 12	<u>1080</u>
	<u>1365</u>

The formulation was prepared by mixing components (a) to (c) under stirring for approximately 15 10 minutes at a temperature of 25°C. Thereafter the concentrate was mixed with component (d) at a temperature appropriate to the filling technique, generally in the range -60 to +20°C. The resulting formulation was a stable solution.

20

Example 2

Solubilisation of salbutamol base

	<u>mg/ml</u>
(a) salbutamol base	2
25 (b) Epikuron 200	14
(c) Propellant 11	339
(d) Propellant 12	<u>1018</u>
	<u>1373</u>

30

=8=

The formulation was prepared as in Example 1 except that solubilisation required stirring for 30 minutes at a temperature of 50°C. A stable solution was formed.

5

Example 3Solubilisation of atropine base

	<u>mg/ml</u>
(a) atropine base	1
10 (b) Epikuron 200	4
(c) Propellent 11	270
(d) Propellent 12	<u>1080</u>
	<u>1355</u>

15

The formulation was prepared as in Example 1 and resulted in a stable solution.

Example 4

20

A series of stable formulations were prepared suitable for use as concentrates in the preparation of aerosol formulations. Each concentrate comprised the following components in the weight ratio of drug : Epikuron 200 : Propellent 11 of 1:14:270. The  
25 drugs used were prednisolone, betamethasone acetate, betamethasone valerate, betamethasone dipropionate and betamethasone free alcohol.

Example 5

30

Solubilisation of formoterol compounds

The following formulations were prepared:

=9=

(i)		<u>mg/ml</u>
	formoterol hydrochloride	0.2000
	ascorbyl palmitate	0.2000
	Epikuron 200	2.7000
5	Propellent 11	341.4125
	Propellent 12	<u>1024.2375</u>
		<u>1368.7500</u>
(ii)		<u>mg/ml</u>
10	formoterol hydrochloride	0.2400
	vitamin E acetate	2.7000
	Epikuron 200	2.7000
	Propellent 11	339.8400
	Propellent 12	<u>1019.5200</u>
15		<u>1365.0000</u>
(iii)		<u>mg/ml</u>
	formoterol hydrochloride	0.1800
	Lipoid S45 Lecithin	2.7000
20	Propellent 11	202.0680
	Propellent 12	<u>1145.0520</u>
		<u>1350.0000</u>
(iv)		<u>mg/ml</u>
25	formoterol base	0.1600
	Lipoid S45 Lecithin	2.7000
	Propellent 11	202.0710
	Propellent 12	<u>1145.0690</u>
		<u>1350.0000</u>
30		

=10=

	(v)	<u>mg/ml</u>
	formoterol hemisulphate	0.1600
	Lipoid S45 Lecithin	2.7000
	Propellent 11	202.0710
5	Propellent 12	<u>1145.0690</u>
		<u>1350.0000</u>
	(vi)	<u>mg/ml</u>
	formoterol fumarate	0.2400
10	vitamin E acetate	2.7000
	Epikuron 200	2.7000
	Propellent 11	339.8400
	Propellent 12	<u>1019.5200</u>
		<u>1365.0000</u>
15	(vii)	<u>mg/ml</u>
	formoterol fumarate	0.2400
	Epikuron 200	2.7000
	Propellent 11	340.5150
20	Propellent 12	<u>1021.5450</u>
		<u>1365.0000</u>

Vitamin E acetate and ascorbyl palmitate were included as antioxidants and did not impair the physical characteristics of the solutions.

The formulations were prepared by mixing the drug, surfactant, Propellent 11 and antioxidant (when present) under stirring for up to 6 hours at a temperature of 45 to 50°C. Thereafter the resulting solution was mixed with Propellent 12 at a temperature appropriate to the filling method to produce a solution.

=11=

Example 6

5 A series of stable formulations were prepared suitable for use as concentrates in the preparation of aerosol formulations. Each concentrate comprised drug, Lipoid S100 and Propellent 11 in the weight ratio of 1:7:135. The drugs used were:

10 Diazepam  
Lorazepam  
propranolol hydrochloride  
hydrocortisone  
fluocinolone acetonide  
15 triamcinolone acetonide

Clear stable solutions resulted in all cases. When matching formulations were prepared omitting Lipoid S100 each drug remained in suspension.

20

Example 7Use of co-solvent to aid solubilisation

A formulation was prepared consisting of xylometazoline hydrochloride, Lipoid S100 and  
25 Propellent 11 in the weight ratio 1:7:135. A matching formulation was prepared in which the Lipoid S100 was omitted. After agitation and heating at 50°C for four hours a considerable amount of drug remained in suspension, in both formulations. Ethanol 4% by weight  
30 was then added to both formulations. After 15 minutes the formulation containing Lipoid S100 was a clear solution. There was no apparent change in the formulation in which Lipoid S100 was omitted. This

=12=

result indicates the efficiency of a small amount of co-solvent in promoting the initial solubilisation step of the phospholipid solubilisation process.

5 Example 8  
Aerosol formulations containing Diazepam

The following formulations were prepared:

		<u>mg/ml</u>	
10 (a)	Diazepam	20	
	Lipoid S100	7	
	Propellent 11	370.5	30%
	Propellent 12	<u>864.5</u>	70%
		<u>1262.0</u>	

15

		<u>mg/ml</u>	
(b)	Diazepam	20	
	Lipoid S100	7	
	Propellent 11	264.3	30%
20	DME	<u>616.7</u>	70%
		<u>908.0</u>	

The formulations were physically stable solutions.

25 Example 9  
Use of Propellents 113 and 115 in solubilised formulations

The following formulation was prepared:

		<u>mg/ml</u>
30	Lorazepam	1.87
	Lipoid S100	13.09
	Propellent 113	252.59

=13=

Propellent 115	126.29
Propellent 22	<u>884.06</u>
	<u>1277.90</u>

- 5 Dissolution of the concentrate containing Lorazepam, Lipoid S100 and Propellent 113 was achieved by heating at 50°C for 10 minutes. Propellent 115 and Propellent 22 were then combined with the concentrate and a physically stable solution resulted.

10

Example 10Use of Propellent 500 (Azeotrope) in solubilised formulation

- 15 The following formulation was prepared:

		<u>mg/ml</u>
	Propranolol HCl	3.02
	Lipoid S100	21.14
	Propellent 11	407.65
20	Propellent 500	<u>951.19</u>
		<u>1383.00</u>

A physically stable solution formulation resulted.

25

Example 11Solubilisation of bitolterol mesylate

The following formulations were prepared:

		<u>mg/ml</u>	<u>mg/ml</u>
30	bitolterol mesylate	4.00	8.00
	Lipoid S100	10.00	20.00
	Propellent 11	201.30	199.20
	Propellent 12	<u>1140.70</u>	<u>1128.80</u>
		<u>1356.00</u>	<u>1356.00</u>

=14=

Solubilisation occurred readily in the Propellent 11/  
lecithin/drug concentrates at room temperature. Both  
solution formulations were stable at -60°C enabling the  
cold filling technique to be employed when preparing  
5 pressurised dispensing packs.

Example 12Solubilisation of Lacicortone

10 The following formulations were prepared:

	(a)	(b)
	<u>mg/ml</u>	<u>mg/ml</u>
Lacicortone	2.00	5.00
Lipoid S100	7.00	14.00
15 Propellent 11	271.20	408.60
Propellent 12	<u>1084.80</u>	<u>953.40</u>
	<u>1365.00</u>	<u>1381.00</u>

Solubilisation occurred readily in the Propellent 11/  
20 lecithin/drug concentrates at room temperature.  
Formulation (a) was stable at -60°C and Formulation (b)  
was stable at -50°C enabling the cold filling technique  
to be employed when preparing pressurised dispensing  
packs.

25

Example 13Use of glycerol phosphatides

The following formulations were prepared:

	<u>parts by weight</u>
30 beclomethasone dipropionate	1
phosphatidyl serine	14
Propellent 11	270



=15=

	beclomethasone dipropionate	1
	phosphatidyl ethanolamine	14
	Propellent 11	270
5	salbutamol base	1
	phosphatidyl serine	14
	Propellent 11	270
	salbutamol base	1
10	phosphatidyl ethanolamine	14
	Propellent 11	270

Each formulation was a stable clear solution suitable for use as a concentrate in the preparation of 15 aerosol formulations.

=16=

## CLAIMS:

1. An aerosol formulation comprising one or more chlorofluorocarbon aerosol propellents, glycerol phosphatide and a drug, the drug being dissolved in the composition.  
5
2. A formulation as claimed in Claim 1, in which the glycerol phosphatide is selected from phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine,  
10 diphosphatidylglycerol, phosphatidic acid and mixtures thereof.
3. A formulation as claimed in Claim 2, in which the glycerol phosphatide is phosphatidylcholine.  
15
4. A formulation as claimed in any preceding claim, in which the glycerol phosphatide is purified.
5. A formulation as claimed in any one of Claims 1  
20 to 4, which comprises Propellant 11, glycerol phosphatide and a drug.
6. A formulation as claimed in any preceding claim, in which the ratio of glycerol phosphatide to  
25 Propellant 11 is 0.01 to 20:100.
7. A formulation as claimed in any preceding claim, in which the ratio of glycerol phosphatide to Propellant 11 is 0.01 to 10:100.  
30
8. A formulation as claimed in any preceding claim, in which the ratio of glycerol phosphatide to Propellant 11 is 0.01 to 3:100.

=17=

9. A formulation as claimed in any preceding claim, which comprises one or more of propellents selected from Propellents 11, 12, 13, 21, 22, 113, 114, 115 and 500.

5

10. A formulation as claimed in any preceding claim, in which the ratio of drug to glycerol phosphatide is 1 to 500:100.

10 11. A formulation as claimed in any preceding claim, in which the ratio of drug to glycerol phosphatide is 1 to 30:100.

12. A formulation as claimed in any preceding  
15 claim, in which the ratio of drug to glycerol phosphatide is 2 to 10:100.

13. A formulation as claimed in any preceding claim, which additionally comprises a small amount of a  
20 co-solvent to enhance the solubilisation process.

14. A formulation as claimed in any preceding claim, in which the drug is selected from beclomethasone dipropionate, betamethasone  
25 dipropionate, acetate, valerate and base thereof, salbutamol base, atropine base and prednisolone.

15. A formulation as claimed in any one of Claims 1 to 13, in which the drug is selected from formoterol  
30 base, hydrochloride, hemisulphate and fumarate.

=18=

16. A formulation as claimed in any one of Claims 1 to 13, in which the drug is selected from diazepam, lorazepam, propranolol hydrochloride, hydrocortisone, fluocinolone acetonide, triamcinolone acetonide,  
5 xylometazoline hydrochloride, bitolterol mesylate and laticortone.

17. A pressurised aerosol pack filled with a formulation as claimed in any preceding claim.

10 18. A method of solubilising a drug having slight solubility in chlorofluorocarbon aerosol propellents which comprises mixing said drug in a chlorofluorocarbon propellant in the presence of an effective  
15 amount of a glycerol phosphatide.

19. A method as claimed in Claim 18, in which the glycerol phosphatide is selected from phosphatidylcholine, phosphatidylethanolamine,  
20 phosphatidylinositol, phosphatidylserine, diphosphatidylglycerol and phosphatidic acid.

20. A method as claimed in Claim 18, in which the glycerol phosphatide is phosphatidylcholine

25 21. A method as claimed in any one of Claims 18 to 20, in which the glycerol phosphatide is purified.

22. A method as claimed in any one of Claims 18 to  
30 19, which comprises Propellant 11, glycerol phosphatide and a drug and the admixture is conducted under stirring.

=19=

23. A method as claimed in Claim 21, in which the ratio of glycerol phosphatide to Propellant 11 is 0.01 to 20:100.
- 5 24. A method as claimed in any one of Claims 19 to 21, which comprises one or more of propellents selected from Propellents 11, 12, 13, 21, 22, 113, 114, 115 and 500.
- 10 25. A method as claimed in any one of Claims 18 to 24, which additionally comprises a small amount of a co-solvent to enhance the solubilisation process.
- 15 26. A method as claimed in any one of Claims 18 to 25, in which the drug is selected from beclomethasone dipropionate, betamethasone dipropionate, acetate, valerate and base thereof, salbutamol base, atropine base, and prednisolone.
- 20 27. A method as claimed in any one of Claims 18 to 25, in which the drug is selected from formoterol base, hydrochloride, hemisulphate and fumarate.
- 25 28. A method as claimed in any one of Claims 18 to 25, in which the drug is selected from diazepam, lorazepam, propranolol hydrochloride, hydrocortisone, fluocinolone acetonide, triamcinolone acetonide, xylometazoline hydrochloride, bitolterol mesylate and lacicortone.
- 30 29. A process for solubilising a drug having slight solubility in chlorofluorocarbon aerosol propellant which comprises using an effective amount of glycerol phosphatide.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 86/00001

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC <sup>4</sup> :    A 61 K 9/72; A 61 K 9/12; A 61 K 47/00		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
IPC <sup>4</sup>	<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> A 61 K 9/00  A 61 K 7/00  A 61 K 47/00 </div> <div style="width: 50%;"> A 61 K 31/00 </div> </div>	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	GB, A, 993702 (TAKEDA) 2 June 1965, see claims; page 1, lines 45-70; page 2, lines 3-45; example 1	1-13, 16-25, 28, 29
A	GB, A, 2001334 (FISONS) 31 January 1979, see claims	1-3, 14, 16
A	US, A, 3551558 (TAKEDA et al.) 29 December 1970, see claim	1-3
A	DE, A, 2802113 (SANDOZ) 26 July 1979, see examples 2, 6	17, 18
-----		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 50%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
17th March 1986		10 APR 1986
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		M. VAN MOL

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO.

PCT/GB 86/00001 (SA 11756)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/04/86

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 993702		None	
GB-A- 2001334	31/01/79	BE-A- 869055 NL-A- 7807625 FR-A,B 2397833 DE-A- 2831419 JP-A- 54035209 AU-A- 3805778 CA-A- 1112567 CH-A- 627075 AU-B- 522792 SE-A- 7807934 SE-B- 443087	17/01/79 23/01/79 16/02/79 01/02/79 15/03/79 17/01/80 17/11/81 31/12/81 24/06/82 20/01/79 17/02/86
US-A- 3551558	29/12/70	None	
DE-A- 2802113	26/07/79	None	

For more details about this annex :  
see Official Journal of the European Patent Office, No. 12/82